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● *Original Contribution*

TRANSTHORACIC ULTRASOUND IN THE EVALUATION OF PULMONARY FIBROSIS: OUR EXPERIENCE

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Abstract—The purpose of this study was to identify the ultrasonographic features of mild, moderate and severe pulmonary fibrosis. Between December 2005 and November 2007, transthoracic ultrasonography (US) was performed by a single operator with specific training in lung sonography on 84 consecutive patients (51 males and 33 females, aged 46 to 73 y) with pulmonary fibrosis. The obtained data were compared with those from a sample of 162 healthy subjects (78 men and 84 women, aged 18 to 76 y). The disease was idiopathic (biopsy confirmed) in 53/84 cases (63%). In the remaining (all histologically confirmed) cases, it was associated with systemic sclerosis ($n = 18$), rheumatoid arthritis ($n = 4$), mixed connective tissue disease ($n = 4$), Sjogren syndrome ($n = 4$), polymyositis ($n = 2$) or primary biliary cirrhosis ($n = 1$). Disease severity was classified as mild, moderate or severe based on clinical findings and the results of standard chest radiography, high-resolution computed tomography and pulmonary function tests. Pulmonary fibrosis was associated with the following US findings: (1) fragmented, irregular thickening ($\mu3$ mm) of the "pleural line" distributed over the whole surface of the lung, especially in the lower posterior lobe (observed in all 84 patients); (2) subpleural cysts (seen in 57/84 (68%) cases of moderate-severe disease); (3) reduction or absence of the physiological "gliding sign" related to disease severity (observed in 33/84 to 39% cases); and (4) increased number of horizontal (and to a lesser extent vertical) reverberation artifacts (seen in 41 patients with advanced fibrosis, 34% of the total series). All abnormalities were detected in both lungs. Although lung biopsy is still the gold standard for diagnosis of interstitial lung disease, transthoracic ultrasound can document early and late-stage changes associated with this disease. (E-mail: sperandeom@libero.it)   © 2009 World Federation for Ultrasound in Medicine & Biology.

Key Words: Pulmonary fibrosis, Transthoracic ultrasonography.

INTRODUCTION

Current estimates indicate that the prevalence of pulmonary fibrosis, which is the end stage of several interstitial lung diseases (ILD), is 10 to 20 cases per 100,000. These figures seem to be on the rise (Martinez et al. 2005) partly as a result of population aging, although improved diagnosis has also played a part. Reported incidence rates range from 3 to 5/100,000 inhabitants per y, with a male:female ratio of 1:1 or 1:2 (Crystal et al. 2002).

ILD is a large, heterogeneous group of nonneoplastic disorders of the lower respiratory tract, sharing some common pathways. The disruption of the alveolar wall leads to progressive loss of functional alveolar-capillary units and the accumulation of collagenous scar tissue, which lead to increasingly severe impairment of ventilation and gas exchange. The progressive disruption of the parenchyma results in secondary lung failure.

ILDs have a number of known causes, including autoimmune disease (rheumatoid arthritis, scleroderma, polymyositis and dermatomyositis, mixed connective tissue disease, relapsing polychondritis, systemic lupus erythematosus); infection (viruses, rickettsias, mycoplasmas, fungi, disseminated tuberculosis); and exposure to mineral dust (silica, carbon, metal dusts, asbestos), organic dust (molds, bird droppings), gases, fumes and vapors (chlorine, sulfur dioxide); therapeutic or industrial radiation; and exposure to drugs and poisons (methotrexate, busulfan, cyclophosphamide, gold, penicilla-

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mine, nitrofurantoin, sulfonamides, amiodarone, paraquat). However, about half of all cases are ultimately regarded as idiopathic (Kim et al. 2006).

Despite their etiologic diversity, the ILDs share a number of clinical, radiographic, pathophysiologic and histologic features. All forms seem to be more amenable to treatment if they are diagnosed early. Unfortunately, the presenting clinical symptoms (dry cough, shortness of breath and reduced exercise tolerance) are insidious and nonspecific, and in many cases, standard chest radiography is almost entirely within normal limits. High-resolution computed tomography (HRCT) is regarded as the imaging modality of choice for ILD diagnosis but it merely provides a more detailed view of what has already been seen on chest radiography (which is very little in the early stages)(Screaton et al. 2005). Pulmonary function testing can be of great value on assessing the response of ILD to therapy but it too reveals nonspecific changes in the initial phases of the disease (Best et al. 2008). Open lung biopsy is still considered by many to be the most reliable method for the definitive diagnosis of ILD. However, although endoscopic variants (*e.g.,* transbronchial biopsy during fiberoptic bronchoscopy, video-assisted thoracoscopic biopsy) have simplified this approach, lung biopsy is still not suitable as a screening method or even a first-line diagnostic procedure because of its invasiveness and susceptibility to possible sampling errors (Hunninghake et al. 2001; JSATS 2002).

Reliable diagnosis of ILD should ideally be based on a combination of clinical and radiologic findings. In this context, the transthoracic ultrasonographic (US) examination might play a useful role. US is an inexpensive, reliable and reproducible imaging technique that is being used increasingly for the study of diseases affecting the pleura and the peripheral regions of the lungs (Decuzzi et al. 2006; Wohlgenannt et al. 2001). Accordingly, transthoracic US could be possibly employed both for the diagnosis and the estimate of the disease severity, and, consequently, as a prognostic tool. A possible role in monitoring of therapy cannot also be excluded.

We investigated the clinical applicability of transthoracic US in 84 consecutive patients admitted to our department between December 2005 and November 2007 with various types of ILD.

MATERIALS AND METHODS

The study population consisted in 84 patients with pulmonary fibrosis (51 males and 33 females, aged 46 to 73 y) admitted consecutively to the internal medicine ward of our hospital between December 2005 and November 2007. In 63/84 cases (75%), the diagnosis of pulmonary fibrosis was made by our staff based on the results of transbronchial biopsy during fiberoptic bron-

choscopy (55 cases) or video-assisted thoracoscopic biopsy (8 cases). In the remaining 21/84 cases (25%), whose disease had already been diagnosed before admission, histology was reviewed by members of the pathology department of our center. Our hospital is a referral center for patients with autoimmune disease and, consequently, over a third (31/84, 36.9%) of the patients considered in this study had pulmonary fibrosis associated with autoimmune pathology, including systemic sclerosis ($n = 18$), mixed connective tissue disease ($n = 4$), rheumatoid arthritis ($n = 4$), Sjogren syndrome ($n = 2$), polymyositis ($n = 2$) and primary biliary cirrhosis ($n = 1$). In the remaining 53 cases (63.1%), the ILD was classified as idiopathic based on transbronchial biopsy findings.

The results of patients were compared with those obtained in a sample of 162 healthy subjects (78 men and 84 women, aged 18 to 76 y, mean age $\pm$ SD: 50.3 $\pm$ 14.6 y), including 38 cigarette smokers and 124 nonsmokers.

All 84 patients also had standard anteroposterior and lateral chest radiography, HRCT and pulmonary function tests. The latter included measurement of the total lung capacity (TLC), forced vital capacity (FVC), functional residual capacity, residual volume carbon monoxide diffusion capacity (DLCO) and oxygen saturation during the 6-min walk test. The severity of the pulmonary fibrosis was rated mild, moderate or severe based on review of combined clinical, functional and imaging findings by one of the authors, as specified in Table 1. Briefly, the disease was categorized as mild if patients had nonproductive cough, total lung capacity between 79% and 90% with normal DLCO test, X-ray evidence of reticular opacities confined to the posterior costophrenic recesses and irregular reticulonodular thickening at HRCT examination. Moderate disease was defined by the presence of exertional dyspnea, total lung capacity between 50% and 70% with DLCO test between 60% and 80%, X-ray evidence of diffuse reticular opacities, HRCT picture of reticulonodular pattern with ground glass opacities and honeycombing in the lower lobes. Severe cases also presented digital clubbing, X-ray with peripheral reticular opacities and honeycombing, HRCT with diffuse bilateral honeycombing, traction bronchiectasis and enlarged mediastinal lymph nodes.

Transthoracic US examinations were performed on all patients by a single operator with specific training in lung sonography (M.S.). A Technos MPX scanner (Esaote, Genova, Italy) was used with convex (3.5-MHz) and linear (8 to 12 MHz) transducers. No preparation of patients is needed before the examination, which can be performed bedside. Patients were examined in the seated position or lying down (supine, prone or lateral decubitus

Table 1. Classification of pulmonary fibrosis based on severity in the 84 patients examined

Severity of fibrosis	Mild (n = 19)	Moderate (n = 32)	Severe (n = 33)
Clinical findings	Nonproductive cough	Nonproductive cough, dyspnea on exertion	Nonproductive cough, dyspnea at rest, digital clubbing
Pulmonary function tests (percentage of reference values)*	DLCO 80%-100%, total lung capacity 70%-90%	DLCO 60%-80%, total lung capacity 50%-70%	DLCO <50%, total lung capacity <50%
Plain film chest radiography	Reticular opacities in posterior costophrenic recesses	Diffuse reticulonodular opacities	Peripheral reticular opacities with honeycombing
HRCT	Irregular reticulonodular thickening	Reticulonodular pattern with ground-glass opacities and asymmetric honeycombing in the lower lobes	Reticulonodular pattern with ground-glass opacities, traction bronchiectasis, more diffuse bilateral honeycombing, enlarged mediastinal lymph nodes

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as needed) and scans were made through all ventral and dorsal intercostal spaces.

In detail multiple scanning planes of US imaging are possible. The posterior thoracic wall can be evaluated with intercostal, longitudinal, transversal or paravertebral scans; the anterior thoracic wall is usually investigated with intercostals, longitudinal, supra-parasternal, subxiphoid and supraclavear scan. Specific acoustic windows are used to better visualize the examined structures, particularly the window offered on the right side of the body by the liver is used to observe the basal pleura and the diaphragmatic dome while the patient in supine is inhaling air; on the left side of the body the acoustic window is offered by the spleen. Images were recorded on photographic film and videotape.

Under the pleura, the US beam will be completely dispersed by pulmonary air; the thin echogenic lining represents the parietal line. First, we evaluate the thickness of this pleural line and the eventual presence of subpleural cysts. Second, we evaluate the gliding sign *i.e.,* the respiratory dependent up and down movement of the pleural line, infarct parietal pleura, does not move

whereas the visceral pleura moves with respiratory acts generating this gliding sign whose frequency can be measured as movements per min. This gliding sign present under physiological conditions needs to be demonstrated in real-time (Reißig and Kroegel 2005); it was first described in the US evaluation of pneumothorax (Wernecke et al. 1987). Finally, we evaluate the presence of reverberation artifacts generated by the difference of acoustic impedance between superficial soft tissues (skin, derma, intercostal muscles, endothoracic membranes and fat pleura) and the air in the lung. The artifacts classified as reverberation are those horizontal concentric hyperechoic lines representing the pleural-thoracic wall interface. Findings were interpreted by the same examiner, who was unaware of the results of other diagnostic procedures performed on the patient.

RESULTS

Based on the classification system summarized in Table 1, 33 of the 84 patients (39.3%) were regarded as having severe pulmonary fibrosis. This subgroup in-

Table 2. Transthoracic ultrasound findings in 84 patients with pulmonary fibrosis of various severities

Severity of pulmonary fibrosis	Ultrasound findings			
	Thickening of the pleural line (>3 mm)	Subpleural nodules	Reduced gliding sign	Increased reverberation artifacts*
Mild fibrosis (n = 19)	• Irregular thickening observed only at the lung base (19/19, 100%) • Bilateral thickening (13/19, 70%)	0/19 (0%)	0/19 (0%)	0/19 (0%)
Moderate fibrosis (n = 32)	• Irregular thickening at both lung bases (32/32, 100%)	24/32 (75%)	13/32 (41%)	16/32 (50%)
Severe fibrosis (n = 33)	• Bilateral involvement in all lung (33/33, 100%)	33/33 (100%)	20/33 (61%)	25/33 (76%)

* Reverberation artifacts are present in the normal lung (Scanlan KA. Sonographic artifact and their origin. AJR 1991;156:1267-1272). This column shows the number of patients with increases in the number of these artifacts with respect to that of a normal lung (Fig. 3).

cluded almost half (26/53; 49.1%) of the patients with idiopathic ILD, one out of three of those whose ILD was associated with systemic sclerosis (6/18; 33.3%), and one of the four patients with mixed connective tissue disease. Moderate fibrosis was found in 32/84 (38.1%) patients, including 19/53 with idiopathic ILD, 7/18 (38.9%) of those whose ILD was associated with systemic sclerosis, both patients with polymyositis, the single patient with primary biliary cirrhosis, one patient with rheumatoid arthritis, one with mixed connective tissue disease and one with Sjogren syndrome. The pulmonary fibrosis was classified as mild in the remaining 19 cases (22.6%): eight patients with idiopathic ILD, five with systemic sclerosis, three with rheumatoid arthritis, two with mixed connective tissue disease and one with Sjogren syndrome.

Table 2 summarizes the transthoracic US findings in the three subgroups of patients. In all 84 patients of the patients we examined, the transthoracic US examination revealed regular or irregular thickening of the pleural line (μ3 mm), which initially appeared at the base of one or both lungs (Fig. 1). On the contrary, no control subject had pleural line thicker than 2.1 mm and no significant difference was found between cigarette smokers ($n = 38$, mean thickness 1.83 ± 0.12 mm, range 1.6 to 2.0) and nonsmokers ($n = 124$, mean thickness 1.84 ± 0.13 mm, range 1.6 to 2.1). Moreover, no difference was found between male ($n = 78$, mean thickness 1.83 ± 0.13 mm, range 1.6 to 2.1) and female ($n = 84$, mean thickness 1.85 ± 0.13 mm, range 1.6 to 2.1) subjects.

Thickness of the pleural line over 3 mm was the only abnormality noted in the 19 patients whose fibrosis had been classified as mild based the criteria in Table 1. In the 32 patients with moderate fibrosis, the pleural thickening was consistently bilateral but it was still confined to the bases of the lungs. Most of the patients in this subgroup (24/32; 75%) also presented subpleural cysts (Fig. 2) and clear enhancement of the horizontal reverberation artifacts that are seen in normal lungs (Kremkau et al. 1986) (Fig. 3). Twenty of 33 of the patients with severe fibrosis presented diminished gliding signs during respiratory movement and the reduction was directly proportional to the severity of the fibrotic disease, with marked slowing in cases of fibrothorax. Reverberation artifacts were also much more frequent in patients with moderate or severe fibrosis.

DISCUSSION

A thorough patient history, aimed at identifying environmental exposure or systemic illnesses known to be associated with damage of the interstitium, is a key starting element in the diagnosis of interstitial lung disease (ILD). Indeed, in the early stages of the disease,
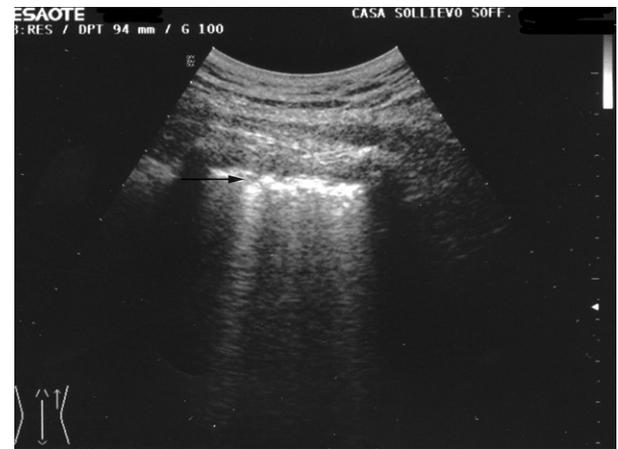
(a)
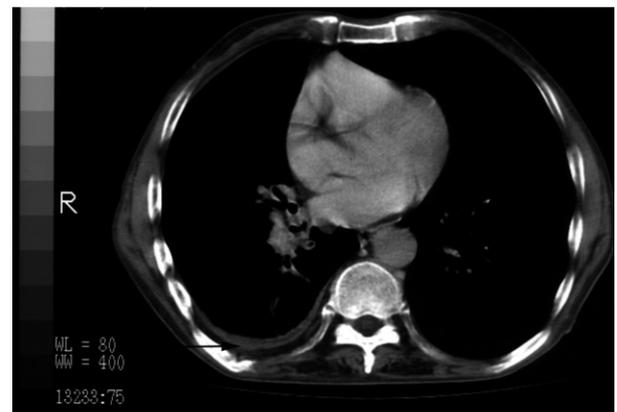
(b)

Fig. 1. (a) Transthoracic US in a patient with mild pulmonary fibrosis reveals only irregular thickening of the pleural line (>3 mm). In most cases, the increased thickness is evident only at the bases of the lungs. (b) The same patient visualized with high-resolution computed tomography (HRCT).

clinical manifestations and radiographic findings may be vague and nonspecific (Selmann et al. 2001). The patient typically presents with one or more of the following: dry, nonproductive cough, dyspnea and fatigue on exertion, clubbing of the digits and crepitant rales at the bases of the lungs. In the absence of specific risk factors, the suspicion of pulmonary fibrosis arises only when other pulmonary and cardiac causes for the patient's symptoms have been ruled out.

The workup at that point includes anteroposterior chest roentgenograms, pulmonary function tests, assessment of the DLCO and a walking test (Egan et al. 2005). Later, HRCT is ordered to confirm the diagnosis of ILD and stage the disease. It is currently considered the most sensitive imaging modality for demonstrating the presence of pulmonary fibrosis although a definitive diagnosis requires surgical lung biopsy (Lynch et al. 2005a, 2005b).
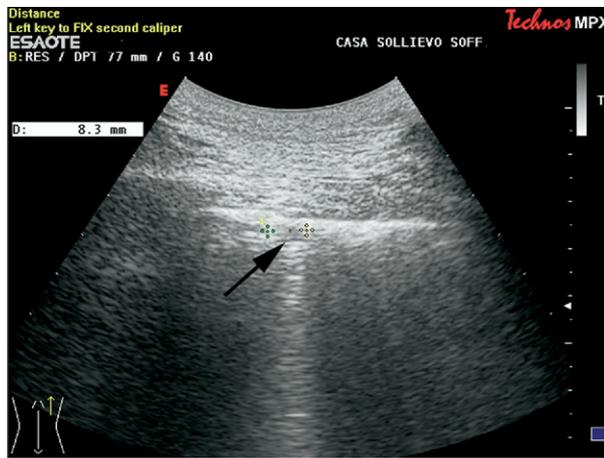
(a)

(b)

Fig. 2. (a) Subpleural cysts were observed in 75% of the patients with moderate pulmonary fibrosis and all of those whose diseases was classified as severe. The cysts ranged in diameter from 0.5 to 2.0 cm. and were located in the middle/basal lung fields. (b) The same patient visualized with high-resolution computed tomography (HRCT).

The method of choice for diagnosis of ILD is an open lung biopsy (Katzenstein et al. 2002), with sampling of tissues from more than one lobe of the lung. Compared with conventional open lung biopsy, those performed during video-assisted thoracoscopy (VATS) or fiberoptic bronchoscopy are much less invasive and equally effective in the diagnosis of ILD. Idiopathic and secondary forms of pulmonary fibrosis share the same basic histologic features, including inflammation of the pulmonary interstitium (infiltration of the alveolar septae by lymphocytes, plasma cells and histiocytes associated with hyperplasia of the pneumocytes); and fibrosis (with

dense acellular collagen and foci of proliferating fibroblasts), areas of honeycombing (fibrotic, cystic air spaces filled with mucus and frequently surrounded by bronchiolar epithelium; smooth-muscle cell hyperplasia) alternating with zones of normal lung tissue. These abnormalities are characterized by spatial and temporal inhomogeneity. The most severe changes are generally found in the lung periphery, in the subpleural and paraseptal regions (Travis et al. 2000).

Lung biopsy is currently recommended for suspected ILD in patients under the age of 50 and/ or those with newly discovered or rapidly progressive disease. For various reasons, however, the risks associated with biopsy procedures (open biopsy or even VATS) may exceed the potential benefits of a definitive diagnosis. For this reason, many patients are diagnosed without pathologic confirmation, based on clinical and radiologic findings alone.

(a)
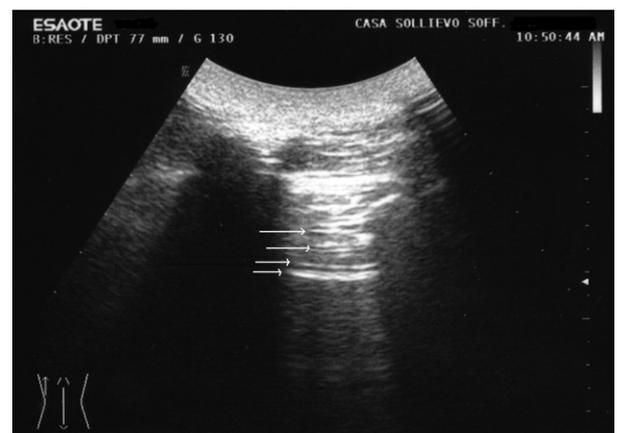
(b)

Fig. 3. Reverberation artefacts (arrows), which are seen in the normal lung (a), are markedly increased in the lung of a patient with severe pulmonary fibrosis (b).

As follow-up, HRCT plays a fundamental role in monitoring the progression of the disease but debate continues on the frequency with which it should be used. Several recent studies (Lama et al. 2003, Lederer et al. 2006) have identified clinical parameters that can furnish reliable prognostic information on the evolution of pulmonary fibrosis. Desaturation during the timed walk test (*i.e.,* a fall in oxygen saturation to 88% or less, during the 6-min walk test) seems to be a strong predictor of mortality within 6 mo of surgical lung biopsy (Lamers et al. 1998). Other studies (Latsi et al. 2003; Uppaluri et al. 1999) indicate that prognostic information can also be obtained by measuring of the FVC 6 mo after lung biopsy.

Transthoracic ultrasonography is now a well established tool for the diagnosis of certain pulmonary diseases (Mathis 1997). In fact, just a decade ago, many physicians shared the mistaken notion that ultrasonography had no utility in chest disease since the US waves are reflected by the bony thorax and are erased to a large extent from the aerated lung. Although thoracic US is not as widely accepted as abdominal US, many recent articles focused on US diagnostic and therapeutic procedures, so that these are currently widely employed in several clinical settings (Sperandeo et al. 2008). Transthoracic US is actually suitable, in common clinical practice, for the workup of patients with diseases of the diaphragm (neoplasms, paresis), of the thoracic wall (abscesses, fistulas, neoplasms), lung (atelectasis, pulmonary consolidation), of the anterosuperior mediastinum (neoplasms, lymphoma, cysts) and of the region between the thorax and the abdomen, and above all, of the pleurae (extrapleural masses, pleural effusions).

Transthoracic US in fact provides good visualization of the peripheral lung tissue and above all the pleura (where most interstitial lesions are found), as well as real-time imaging of respiratory movements and it is also low-cost, widely available, repeatable, and associated with high reproducibility. Given these premises, we investigated the possible role of thoracic US in the clinical workup of patients with ILD. Based on our examination of 84 patients with varying degrees of pulmonary fibrosis, idiopathic or secondary to autoimmune disease, we believe that thoracic US can provide potentially useful information regarding the structural and functional changes provoked by ILD, even in the early stages of the disease. In patients with mild disease, the only sonographic anomaly observed was irregular thickening of the pleural line (μ3 mm thick), which was confined to the lung base and in many cases bilateral. In this regard, our results on healthy subjects, in line with data from literature (Mathis 1997) are noteworthy since controls never had pleural lines thicker than 2.1 mm, irrespective of gender and cigarette smoking. Thus, no false positive

was found utilizing such a conservative cut-off limit for pleural line thickening. On the other hand, using the same cut-off, at least an irregular thickening was found in all patients, which suggests an exceedingly high sensitivity. This result, if confirmed on larger series, would deserve particular emphasis since in most of these cases conventional chest X-rays and pulmonary function testing in these patients were completely uninformative. In patients with more advanced fibrosis (moderate or severe, according to our classification), pleural thickening became progressively more pronounced and extensive, involving the entire pleura. Severe fibrosis was also strongly associated with diminished gliding signs during respiratory movement and these reductions were proportional to the severity of the fibrotic disease.

In light of this experience, it is possible to envision useful complementary roles for transthoracic US in various phases of the diagnosis and management of ILD. For example, a "screening" US could be done when the first suspicion of ILD arises (especially in patients with known predispositions to the disease). Conventional roentgenograms of the chest are often negative in these cases and, while HRCT is undeniably sensitive in the diagnosis of ILD, it is considerably more expensive than a chest X-ray and may not be available in small centers. It also exposes the patient to a higher dose of ionizing radiation. In contrast, transthoracic US can reveal pleural thickening even in the early phases of ILD, without exposing the patient to any radiation, and it is both economical and widely available. In the absence of other causes, US findings of a pleural line exceeding 3 mm in thickness should direct the workup toward the possibility of ILD, which can be best evaluated with HRCT, functional testing and ultimately lung biopsy. This approach might result in earlier diagnosis (although it remains to be seen whether early diagnosis has any real impact on the prognosis quoad vitam) and more rational use of healthcare resources.

Thoracic ultrasonography can also be repeated easily and this makes it an ideal method for monitoring the evolution of the disease and patients' response to treatment. We found that, in all phases of ILD, thoracic US can be useful for detecting and quantifying thickening of the peripheral lung interstitium. Although the US features we documented are not always specific for ILD, they show good correlation with the degree of fibrosis. In fact, in patients with clinically severe disease, the abnormalities observed on US were more numerous and more evident.

The results of this preliminary experience are encouraging and it is to be hoped that the potential of US for the diagnosis and follow-up of ILD will be evaluated in large, multicenter studies.

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